Virologie de l'hépatite C

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Virologie de l'Hépatite C

Under the supervision of the following institutions and research bodies:

Université Paris Descartes

December 2012

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

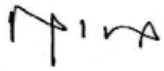
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



Pierre Glaudes

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

Grading

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

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

With respect to this score, the research unit concerned by this report received the following grades:

- Grading table of the unit: Virologie de l'Hépatite C

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

Evaluation report

Unit name:	Virologie de l'hépatite C
Unit acronym:	
Label requested:	EA
Present no.:	EA 4474
Name of Director (2012-2013):	Ms Arielle ROSENBERG
Name of Project Leader (2014-2018):	Ms Arielle ROSENBERG

Expert committee members

Chair:	Mr Jean DUBUISSON, University of Lille
Experts:	Mr Patrice ANDRÉ, University of Lyon 1
	Mr Jacques IZOPET, University Paul Sabatier, Toulouse
	Mr Philip MEULEMAN, University of Ghent, Belgium

Scientific delegate representing the AERES:

Mr Jean ROSENBAUM

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

Mr Frédéric DARDEL, University Paris Descartes

1 • Introduction

History and geographical location of the unit:

The unit was created as an "Equipe d'Accueil" (EA-4474) in January 2010, at the end of the Inserm AVENIR contract of the principal investigator of the team. It is located at the Institut Cochin, at the University Paris Descartes.

Management team:

AERES nomenclature :

SVE1_LS6 Immunology, microbiology, virology, parasitology

Unit workforce:

Unit workforce	Number as at 30/06/2012[1]	Number as at 01/01/2014[2]	2014-2018 Number of project producers[3]
N1: Permanent professors and similar positions	1 (0.50)	1 (0.50)	1
N2: Permanent researchers from Institutions and similar positions			
N3: Other permanent staff (without research duties)	2 (0.60)	3 (0.90)	2
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)		1	
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**3** (1.10)	**5** (2.40)	**3**

Percentage of producers	%

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	3	
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	2	3

2 • Assessment of the unit

Strengths and opportunities:

The team has a unique position and expertise with the culture system to propagate hepatitis C virus in primary human hepatocytes. With the development of this culture system, the team has acquired a very good visibility at the international level. This led also to unique opportunities for the team to collaborate with excellent groups worlwide. The head of the unit has a strong leadership and there is a very good cohesion within the team. Finally, the project, based on the expertise of the group, is intersting and well focused.

Weaknesses and threats:

Although the size of the team has increased since the last evaluation, it remains rather small, and it is only supported by the strong leadership of its leader. The team lacks permanent scientists and permanent technician(s)/engineer(s). The presence of a permanent technician/engineer would be helpful for the team to keep the memory of the laboratory.

Recommendations:

The committee encourages the team to follow on with its projects.

3 • Detailed assessments

Assessment of scientific quality and outputs:

The main success of this team during the last term is the establishment of a new culture model of hepatitis C virus (HCV) entry, replication and virion production. This system is based on culture of primary human hepatocytes infected with cell culture derived HCV (HCVcc), derived from the JFH1 HCV strain and derivatives. Interestingly, HCV viral particles produced with this system have a higher specific infectivity that correlates with a lower density than the same viral particles produced by the hepatoma cell line Huh-7 and are thus closer to the particles isolated from plasma of infected individuals. The model is indeed an interesting breakthrough with many potential applications, and it was published in Gastroenterology in 2010.

The model in a way remains a specific knowhow of the team since many other laboratories could not reach the same expertise and success in producing the virus with primary human hepatocytes. This expertise provided multiple opportunities to collaborate with other teams in search of more physiologically relevant models of HCV replication than hepatoma cell lines. In particular, the model helped to validate the role of diacylglycerol-acyltransferase-1 (DGAT1) in targeting the viral core protein to lipid droplets, to study the mechanism of the epithelial-mesenchymato-transition, the modification of the innate immune response by HCV or the effect of alcohol on viral replication and lipid synthesis. These collaborations led to either publications in high-ranking journals or communications at international meetings.

The team is composed of 1 MC-PH and two PH. It has publised 12 papers directly related to the project, among which 4 have first and/or last authors from the lab, including the Gastroenterology (IF ≈12). Members of the team are also coauthors in high-ranking journals (1 Nature Medicine, 1 Gastroenterology, 1 J Exp Med, 1 Hepatology, 1 Journal of Hepatology,…). In addition, the team members have also published 33 other papers on subjects not directly related to the project.

Assessment of the unit's academic reputation and appeal:

With the development of a more physiological cell culture model for HCV, the team had the opportunity to collaborate with internationally renowned teams and this led to excellent publications in the context of these collaborations. More recently, a new collaborations have also been initiated with a NIH laboratory. It is worth noting that the team of Ms Arielle ROSENBERG remains the only one able to successfully propagate HCV in primary human hepatocytes, and this provides the group with a unique position in a very competitive field of research.

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

Team members have produced several reports of expertise (4). They have also published 2 papers in scientific popularization journals. Finally, the team has also a good connection with medical diagnostics.

Assessment of the unit's organisation and life:

The leader of the team has a strong leadership, and there is an excellent cohesion within the group. There is also a very good supervision of the students and a good follow up of the students in connection to their integration into the job market.

Assessment of the unit's involvement in training through research:

Two members of the team have their HDR and 3 theses have been defended during the past 5 years. One PhD student and a M2 student have recently been recruited. Several students from a school of technicians/engineers have done their internship in the laboratory. There is a good evolution in the career of the former PhD students: 1 became MCU-PH, 1 did a post-doc at NIH and is now back in the lab for a second post-doc and the third one who recently defended her thesis remains post-doc in the team before going abroad for a post-doc.

Assessment of the five-year plan and strategy:

The backbone of the scientific project will continue to rely on the HCV culture model in human primary hepatocytes with three major specific objectives. The aim of the first objective is to decipher the role of the VLDL pathway in the biogenesis and assembly of viral particles with the additional effect of alcohol on the VLDL and viral biogenesis. The second is the study of the cellular partition of neutral lipids between the cytosolic and ER lumen compartments, HCV being used as a tool to modulate the balance. Finally, the third objective aims at testing direct active antiviral (DAA) efficiency and toxicity.

Since the HCV life cycle is tightly linked to the lipid metabolism, it is indeed relevant to further describe and understand how the virus may benefit from lipids at each step of its life cycle in various cell conditions. In addition, it is also important to determine how the virus modifies the cell metabolism to fulfill its needs. The culture model developed by the team is probably the most relevant system to study in vitro the apoB positive lipoprotein function and biogenesis. It is thus the most appropriate not only to prove the apoB recruitment on the virion and its role in infectivity, but also to analyze the contribution of the major key cellular factors of the VLDL biogenesis in virion morphogenesis. In addition, the culture system may prove a good model to study the effect of ethanol on the lipid metabolism in the context of HCV infection. The project will benefit from the expertise in lipid droplet analysis acquired by the post-doc fellow when she was at the NIH as well as from collaborations with experts in the field of lipidomics.

The third objective proposes to test anti-viral molecules in the primary human hepatocyte culture system, and particularly the direct active antivirals (DAA) to test the best molecule combinations. However, it is not clear what would be the advantage of the primary human hepatocyte culture system over the current HCVcc model to test these DAAs. The human primary hepatocyte model would be more appropriate for testing indirect acting antivirals that could be tested in diverse human genetic backgrounds and in more physiological metabolic conditions than with hepatoma cell lines.

Finally, the projects are supported by specific grants.

4 • Conduct of the visit

Visit dates

Start: December 6, 2012, at 10 am

End: December 6, 2012, at 4 pm

Visit site: Hôpital Cochin

Institution:

Address: 27 rue Du Faubourg Saint Jacques, Paris

Conduct or programme of visit:

10h00 - 10h30	Huis clos - Présentation de l'AERES au Comité de visite par le Délégué Scientifique
10h30 - 10h45	Devant l'unité, présentation du Comité de visite et présentation de l'AERES par le Délégué Scientifique
10h45 - 12h00	Présentation de l'unité par le Directeur (bilan et projet) et discussion scientifique
12h00 - 12h30	Session rencontre avec le personnel permanent et non permanent
	Rencontre avec les post-doc, doctorants et autres stagiaires Auditoire : membres du Comité, Délégué AERES, sans la Tutelle, ni le Directeur
	Rencontre avec le personnel permanent Auditoire : membres du Comité, Délégué AERES, sans la Tutelle, ni le Directeur
12h30 - 13h30	Déjeuner
13h30 - 13h45	Rencontre avec le représentant de la Tutelle (Université Paris Descartes) Auditoire : membres du Comité, Délégué AERES
13h45 - 14h00	Rencontre avec le Directeur de l'unité Auditoire : membres du Comité, Délégué AERES
14h00 - 16h00	Réunion du comité à huis clos Présence : membres du Comité, Délégué AERES

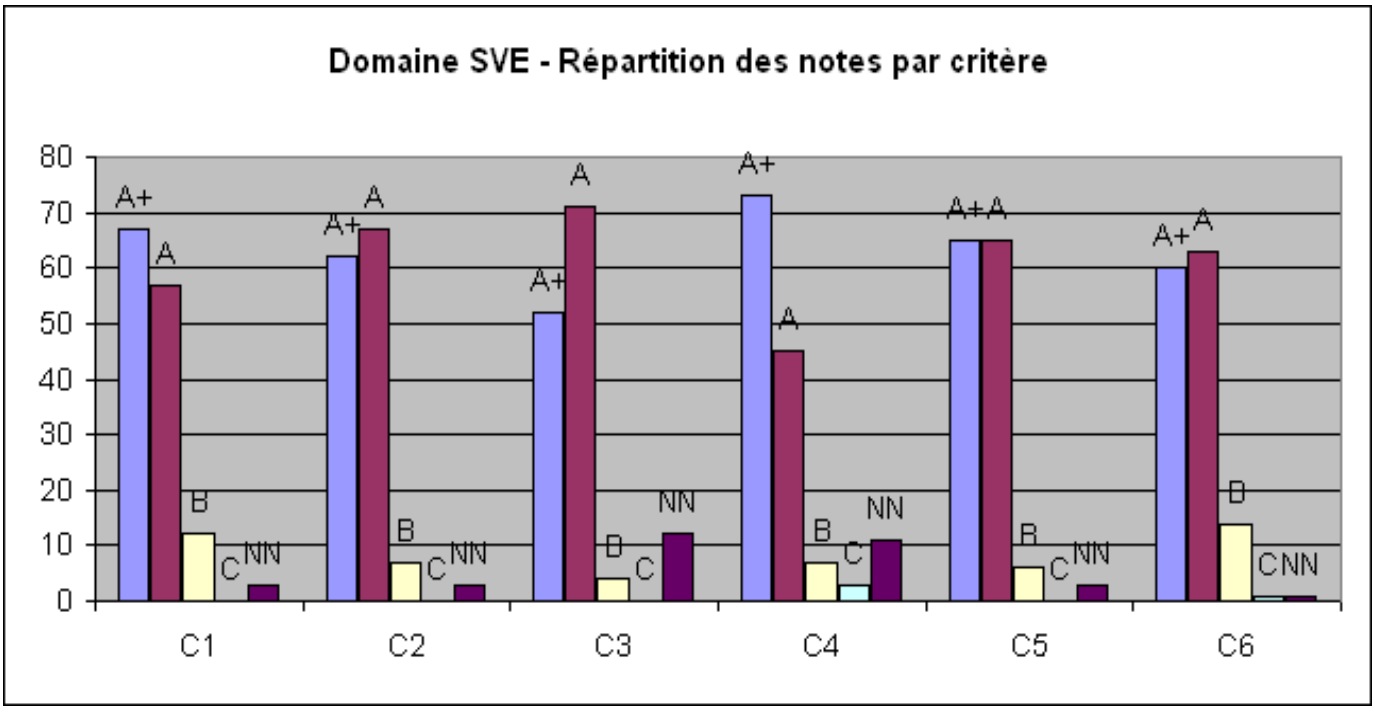
5 • Statistics by field: SVE on 10/06/2013

Notes

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

Pourcentages

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



6 • Supervising bodies' general comments

UNIVERSITÉ PARIS DESCARTES

Vice Président du Conseil Scientifique

Paris le 22.03.2013

Vos ref : S2PUR140006283 –
Virologie de l'hépatite C - 0751721N

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
Agence d'Evaluation de la Recherche et de l'Enseignement Supérieur
20, rue Vivienne
75002 PARIS

Monsieur le Directeur

Je vous adresse mes remerciements pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise concernant l'unité « Virologie de l'hépatite C »

Vous trouverez ci-joint les réponses du Directeur de l'unité, Arielle ROSENBERG.
Nous sommes conscient du manque récurrent de personnel temps plein dans les équipes de recherche qu'il est impossible de régler dans la globalité. C'est pour cette raison que nous encourageons les directeurs d'EA, quand cela est possible, de rejoindre des UMR. Pour cette équipe particulière, qui dans la période récente a significativement amélioré sa production scientifique, nous essayerons de favoriser son intégration à une UMR ou un centre sur un des sites de Paris Descartes.

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

Le Vice Président du Conseil Scientifique

Stefano Marullo, DM, DesSci

Université Paris Descartes, Vice-présidence du conseil scientifique, 12 rue de l'école de médecine, 75170 PARIS cedex 06
Téléphone: 01 76 53 17 45; Courriel: stefano.marullo@parisdescartes.fr

UNIVERSITÉ PARIS DESCARTES

Arielle R. Rosenberg, M.D., Ph.D.
Directrice, EA 4474 "Virologie de l'Hépatite C"
Institut Cochin, Bât. Méchain, 2e étage, p. 234A
22 Rue Méchain, 75014 Paris, France
Tél: +33 1 40 51 64 93
arielle.rosenberg@parisdescartes.fr

EA 4474 « Virologie de l'Hépatite C »

Observations de l'unité sur le rapport d'évaluation de l'AERES

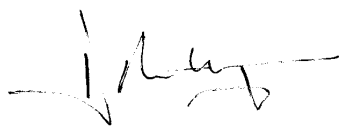
En mon nom et en celui des membres de l'équipe, je souhaite remercier très sincèrement le président et les experts du comité de visite pour leur rapport d'évaluation à la fois sérieux, compétent et constructif.

Nous percevons comme un encouragement de grande valeur le fait que ce comité, composé d'experts renommés dans le domaine très compétitif de la recherche sur le virus de l'hépatite C, reconnaisse le positionnement international qu'a su acquérir notre jeune équipe en développant un système expérimental qui reste aujourd'hui unique en ce qu'il permet la culture de ce virus dans des hépatocytes humains primaires. C'est donc avec enthousiasme que nous nous engageons à suivre sa recommandation de persévérer dans nos projets focalisés sur la base de ce modèle pertinent.

La formation des doctorants a toujours été l'une de nos priorités, et nous sommes donc particulièrement sensibles aux remarques du comité concernant la qualité de leur encadrement au sein d'une équipe soudée, ainsi que la bonne évolution des étudiants formés au laboratoire, qui tous ont pu poursuivre leur carrière selon leurs vœux.

Enfin, nous ne pouvons qu'adhérer au commentaire sur le manque de chercheurs et techniciens/ingénieurs de notre petite équipe, que nous avions nous-mêmes souligné dans notre auto-évaluation, et nous espérons donc que notre tutelle tiendra compte de la recommandation du comité en nous aidant effectivement à recruter au moins un titulaire.

Fait à Paris, le 17/03/2013



Arielle ROSENBERG