MAVIVH - Morphogénèse et antigénicité du vih et des virus des hépatites

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Morphogenesis & Antigenicity of HIV and Hepatitis Virus

From the

University François Rabelais – Tours

INSERM

December 2010

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

December 2010

Research Unit

Title: Morphogenesis & Antigenicity of HIV and Hepatitis Virus

Requested label : UMR_S INSERM

N° in the case of renewal : U 966

Name of the director : M. Philippe ROINGEARD

Members of the review committee

Committee chairman:

M. Denis GERLIER, Université de Lyon 1, France

Other committee members:

M. Ralf BARTENSCHLAGER, University, Heidelberg, Germany

Ms Aine McKNIGHT, Queen Mary University of London, London, UK

M. Renaud MAHIEUX (CSS INSERM), ENS Lyon, Lyon, France

Ms Jacqueline CAPEAU (CNU), Université Pierre & Marie Curie, Paris, France

Observers

AERES scientific advisor:

M. Yves GAUDIN

University, School and Research Organization representatives :

M. Michel ISINGRINI (Vice-President for research François Rabelais University)

Ms Christine TUFFEREAU (INSERM, DESP)

Ms Marianne DESMET (INSERM Regional Delegate)

Report

1 • Introduction

- **Date and execution of the visit:**

The visit was held on December 10th 2010. The visit started with a general presentation by the head of the lab of the main achievements and the future organization and orientations. The Principal investigators presented the results and projects and had to answer many questions. The committee auditioned separately the students and post-docs, the scientists and the technical and administrative staff. The committee then met with representatives from Tours University and INSERM. A closed-door meeting of the committee to prepare the present report concluded the visit.

- **History and geographical localization of the research unit, and brief presentation of its field and scientific activities:**

The joint University of Tours - INSERM U966 is re-evaluated this year for in frame coordination with the University five year plan due to start in January 2012. This unit was created in 2009 as the logical development of the INSERM labelled ERI 19 under an ESPRI contract sponsored by both INSERM and the Région Centre during the 2006-2008 period. This virology laboratory has an history back to the early eighties with the development of the first vaccine against the hepatitis B. The laboratory is located in the Medical Faculty building.

The research field of the U966 aims at analysing viral morphognesis and antigeniticity of virus quasi-species of two human pathogens, HIV-1 and hepatitis C virus (HCV). A first goal is to revisit the HIV assembly and morphogenesis using primary isolates in search for more physiologically relevant information. A second goal is to understand how HCV hijacks the host cell lipid metabolism for HCV genome encapsidation and assembly on internal cell membranes and virus release. The third goal is to understand how HIV-1 and HCV quasi-species are selected in human patients to escape neutralizing antibodies with the hope to design optimal immunogen inducing broadly reactive antibodies.

- **Management team:**

The Unit is directed by P. ROINGEARD, Director, assisted by one deputy-director (F. BARIN) and one secretary. The unit council is made of 5 University Full Professors (PU-PH, PU-Prat Att), 3 Assistant Professors (MCU-PH, MCU) and 2 hospital practitioners and is headed by the Unit Director.

- **Staff members (on the basis of the application file submitted to the AERES):**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	**8**	**11**
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	**0**	**0**
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	**8**	**7**
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	**6**	**6**
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	**0**	**0**
N6: Number of Ph.D. students (Form 2.7 of the application file)	**8**	**9**
N7: Number of staff members with a HDR or a similar grade	**6**	**7**

2 • Overall appreciation on the research unit

- **Summary:**

The unit belongs to the group of few laboratories working in strong and successful interaction with the clinics and epidemiologic bodies (National reference center for HIV). This unique interaction offers a healthy environment with novel concepts and a strong platform for translational research. The overall appreciation of the unit was very good. Some parts of the project are stronger with higher production prospects, and those parts may merit more focus.

- **Strengths and opportunities:**

- Prediction of virus transmission and/or maintenance of long term non-progressor status analysing of the neutralising antibody response in humans.

- Original studies on unique cohorts of HIV and HCV infected patients including mother to child transmission.

- Unique expertise (with international profile) in the evaluation of neutralising antibodies against the HIV MBA strain.

- Novelty of a promising HBV based vaccine approach against HCV and HIV with a strong industrial support.

- Original research on steatosis induced by HCV infection using clinical biopsies from the local hospital.

- Extremely interactive team with successful crossfertilisation between two sets of complementary expertises.

- The team benefits from the strong support of Tours University. Notably, 5 permanent faculty positions have been allocated since 2006.

- **Weaknesses and threats:**

- Lack of researchers without teaching duties.

- HIV Vaccine development would add substantially to the strength of the unit but critically needs additional support from National and International funding agencies.

- **Recommendations:**

- To focus on the major promising projects to maintain the competitiveness of the team by speeding up the progress and possibly increasing their international impact.

- To be more active at the international level, in particular by looking for EU fundings although the committee is aware of how little funding is available for HIV vaccine development.

- **Production results:**

(cf. http://www.aeres-evaluation.fr/IMG/pdf/Criteres_Identification_Ensgts-Chercheurs.pdf)

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	8
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	0
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	2
A5: Number of PhD granted during the past 4 years	7

3 • Specific comments

- **Appreciation on the results:**

The Unit focus is on viral morphogenesis, HCV-induced pathogenesis, especially steatosis, and HIV and HCV diversity as an escape mechanism from the neutralizing antibody response. Although these two projects have been separately presented during the oral presentation, they are tightly interconnected. Hence, the visiting committee has performed a combined analysis in line with the document describing the 2006-2010 activity report and the 2012-2016 project.

Concerning virus morphogenesis studies, the group addresses relevant aspects on two medically highly relevant viruses. This includes studies of HCV assembly, HCV RNA genome packaging, HCV-induced steatosis, HCV-triggered changes of intracellular membranes, construction of HBV-HCV chimeric particles that might be suitable as an HCV-specific vaccine, and HIV morphogenesis.

Regarding HCV, the role of core protein in inducing steatosis appears most interesting, relevant and promising for continuation and part of it has already been well published. The proposed plan on how to continue this subproject is very good and convincing. Here one can expect consistent output with clinically relevant results. In this respect, the correlation of the in vitro data with analyses of liver biopsies from patients is excellent.

Also promising are the results on HBV/HCV chimeric particles that led to an international patent and a strong grant support from a company. The vaccine candidate is now followed up together with this company in order to determine immunogenicity in small animal models. Thus, this successful project with sound and solid proposed continuation is in the needs of further grant support for translation research.

The other HCV projects are technically more challenging and given inherent limitations, depend on more artificial experimental approaches. For instance, the Semliki Forest virus replicon appears to allow the detection of structures resembling HCV-like particles. The team is aware of the limitations of this experimental system and has proposed important validation studies with state-of-the-art assays.

Likewise, because it is necessary to uncouple replication from assembly, the project dealing with genome packaging also has some limitations that the team is aware of. The group might consider backing up the data obtained in this cell culture system by using in vitro assays such as direct RNA – core protein interaction measurements (e.g. by using BiaCore, Gel-shift or other).

The project dealing with HCV and apolipoproteins is strong and builds on earlier studies on the association of HCV particles with apoC1. It is a logical continuation of previous work and has a high chance for success.

Finally, the project dealing with HIV assembly at the plasma membrane vs. intracellular membranes is also very strong. Nevertheless, the authors might search for an additional proof for the real assembly site before going into very challenging lipidomics analysis.

The clinical observation of naturally occurring compensatory Env mutations in the HIV matrix gene associated with Env mutations leading to truncated cytoplasmic tails may pave the way for considering Env-MA interaction as a possible target for antiviral therapy.

Related to HIV, the applicants want to study the relationship between evolution of Env variants and sensitivity to neutralization. Importantly, the applicants take advantage of an important collection of samples from long-term non-progressors, which is very pertinent to study the changes of Env variants over time of immune selection.

HIV neutralization will be also addressed in two additional subprojects. First, a correlate of immune protection will be further analyzed in the setting of mother-to-child transmission using two larger cohorts to which the applicants have now access. Second, cell-based assays will be used to identify regions in HIV Env (strain MBA) targeted by selected neutralising antibodies. Neutralising sites are expected to be identified by screening neutralising antibody for their binding to random linear peptides expressed by phage display. However, from what has been reported many times with this approach, the information that can be expected by such screening looks rather limited.

Similar aspects are also studied for HCV infection by using well established methods such as HCVpp and infection of Huh-7 cells. Again, the strength is the use of clinically relevant samples, i.e. series of samples from patients during the acute, and later on, the persistent state of infection, as well as paired donor and recipient samples from needle stick injuries. In addition, HCV variant evolution in relation to maternal antibodies will be studied by using samples obtained from a collaborator in Thailand (mother-to-child transmission).

The team's research, described above, has already been very productive with 15 publications since 2006, including two leading papers in Gut (2007) and in Lancet Infect. Dis. (2010), 3 J. Infect. Dis., 3 J. Virol., 2 Virology, 2 J. Gen. Virol., 2 AIDS, 1 J. AIDS and 1 Cell. Microbiol. Seven students have got their PhD, all of them with at least one paper as first author in a very good journal in virology and three scientists got their HDR between 2006 and 2010. Three patents have been granted. One has attracted the interest of a company which has provided a grant for further development. The team has been very active in diffusion of science culture among the public with elaboration of excellent pedagogic tools for every year "Science Feast".

The unit has several fruitful mainly national collaborations with a total of 37 publications, a third of them in the best journal in the field. For example, the EM virus morphogenesis expertise of the team has led to several very good publications including 1 PLOS Pathogens, 1 J. Mol. Biol., 6 J. Virol. 1 Retrovirology, 2 J. Gen. Virol. Other expertises from the team have been recognized through other publications including 1 PNAS. A particularly strong partnership is ongoing with the Chiang Mai University (Thailand).

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners:**

Unit members have given a dozen of guest lectures in international congress or meetings.

Funding of the unit has been regularly on good grounds with many grants from the ANRS, SIDACTION, INSERM-DHOS, Region Centre, and a grant from a company consecutive to a new very promising patent.

Students and post-docs have been recruited both locally and from abroad (Italy, Thailand). Notably, the selection procedure for "Region Centre" supported PhD fellowship is advertised on the web which attracts the best students.

The unit is an active and strong member of loco-regional federative structures namely the Cluster in Infectiology and the IFR of Infectiology, the later one regrouping about 200 scientists or faculty members.

- **Appreciation on the management and life of the research unit:**

The management quality of the research unit is exceptionally good. Every member, whichever his/her status and function, is well associated to every aspect of the life of the unit. Senior and junior scientists are responsible for their own projects that are highly interconnected and for which they are applying for funding. Priorities are decided on a common basis after everyone exchanges ideas. Students and technicians are fairly acknowledged on publications and presentations at national and international meetings. PhD students write the first draft of papers describing their work. The staff benefits from a continuous education. Internal resources and collections are managed using a server-based dedicated software. In short, the research unit exhibits a rare climate associating studiousness, professionalism and happiness.

Staff members are deeply involved in teaching in the local university. All members are teaching in Master course in Infectiology. The head of the Unit is responsible for the PhD program Health Biological Sciences and Chemistry (350 students) in common to Tours and Orleans Universities. The unit is active member of the IFR 136 in Infectiology, with members of the team driving the electron microscope facilities and one member will co-head the future SFR structure that will replace the IFR for the next five year period.

- **Appreciation on the scientific strategy and the project:**

The overall project is sound and mostly feasible using original and pertinent tools in particular because of their access to clinical samples and well defined cohorts of HIV and HCV infected patients. The main questions asked are highly pertinent, and the research design is likely to be most informative.

The proposed plan to continue the role of HCV core protein in inducing steatosis is very good and convincing with obvious clinically relevant outputs thanks to the planned correlations with liver biopsies from patients.

The demonstration that the vaccine candidate based on HBV/HCV chimeric particles can induce cross-neutralizing antibodies in small animal models will be a key step in the validation of this new promising vaccine prior to additional preclinical trials and finally protective trials in a primate model.

The ongoing HIV and HCV project on tracing viral Env glycoprotein diversity and evolution against the continuous onset of neutralising antibodies during natural infection places the team at the very forefront of the international efforts to design a potent HIV and HCV vaccine aiming at inducing a neutralising (hopefully protective) antibody response. Further clues on the impact of neutralizing antibodies on the control of virus burden are likely to be obtained. Moreover, the chimeric HIV-Env-HBs construct designed as a vaccine candidate fully warrants further exploration and support from national and/or international bodies such as the Bill and Melinda Gates Foundation to which an application is pending, as it represents a really novel promise for an anti-HIV vaccine.

From the high quality of the management shown in the previous period, there is no doubt that the resources will be properly allocated with higher priority to the most cutting edge and promising projects.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
MORPHOGENÈSE ET ANTIGÉNICITÉ DU VIH ET DES VIRUS DES HÉPATITES (MAVIVH)	A	A	A+	A+	A

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- **SVE1 Biologie, santé**
  - **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
  - **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
  - **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
  - **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
  - **SVE1_LS5 Neurosciences**
  - **SVE1_LS6 Immunologie, Infectiologie**
  - **SVE1_LS7 Recherche clinique, Santé publique**
- **SVE2 Ecologie, environnement**
  - **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
  - **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
  - **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

Date : Tours, March 21, 2011
From : Pr Philippe Roingeard, Head, INSERM-University Unit U966
Re : AERES Report « B2012-EV-0370800U-S2UR120001557-RT-ROINGEARD » (rapport d'évaluation de l'unité Morphogenèse et Antigénicité du VIH et des Virus des Hépatites -MAVIVH-)

Dear Members of the AERES Review Committee,

On behalf of myself and all members of the research unit, we thank the Committee for their visit and review of our work. We were pleased by the positive evaluation of our accomplishments and projects, as well as the constructive advices on our current research efforts.

We would like to briefly comment on two points:

- The recruitment of one full time permanent research scientist without teaching duties remains a key priority for the team. This year, one post-doc from the team has been selected for an oral presentation of its project by two different Inserm commissions and we hope that its application to a permanent position (CR1) will be successful.

- Although this is a minor point, we wish to precise the statement made on the counting of our publications, page 6: The number of 15 does not represent the number of publications since 2006 but the average number of publications per year over the period 2006-June 2010. Over this period, the unit has indeed published 32 manuscripts related to the unit own work, and 35 manuscripts made in collaborations with national or international teams.

Again, we thank you for your confidence and support of our research efforts.

Yours sincerely,

Philippe Roingeard

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