UMI - Biologie structurale des intéractions entre virus et cellule Hôte

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Virus Host Cell Interactions

From the

University Grenoble 1

CNRS

EMBL

Mai 2010

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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

Mai 2010

Research Unit

Name of the research unit: Virus Host Cell Interactions (UVHCI)

Requested label : Unité Mixte Internationale (UMI)

N° in the case of renewal: 3265

Name of the director: Stephen CUSACK

Members of the review committee

Chairperson

M. Félix REY, Institut Pasteur Paris, France

Other committee members

M. Hans-Georg KRAEUSSLICH, Universität Heidelberg, Germany

M. Nuria VERDAGUER,Institut de Biologia Molecular de Barcelona, Spain

M/ Kay GRÜNEWALD, Oxford Particle Imaging Centre, United Kingdom

Committee members nomminated by staff evaluation committees (CNU, CoNRS, INSERM and INRA CSS....)

Ms. Isabelle MUS-VETEAU, CoNRS member

Observers

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Research Organization representatives

M. Thierry MEINNEL, CNRS

M. Silke SCHUMACHER, Head of International Relations and Communications, EMBL

Report

1 • Introduction

- Date and execution of the visit

The visit took place on February 8, 2010, from 8AM to 7PM. After an introduction by the AERES Delegate and a brief presentation of the Evaluation Committee, there was a presentation by the Head of the Unité Mixte Internationale (UMI), describing the history, context and main events that led to creation of the UMI in 2008. Each of the group leaders then presented their results and main projects, followed by questions from the committee. The session continued with an interview of the Committee with laboratory members in three sections (techniciens and administrative personnel, then post-docs and graduate students, and then staff scientists and engineers). This was followed by a meeting with the representatives from the different organisms running the UMI (see below), and finally a meeting of the committee with the Director and Deputy Director of the UMI. The committee then deliberated for 2h to discuss the main impressions and to draft a preliminary report.

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

The evaluated laboratory is only part of the UMI, which is jointly run by the Université Joseph Fourier (UJF) of Grenoble, the Centre National de la Recherche Scientifique (CNRS) and the European Molecular Biology Laboratory (EMBL). The UMI is composed of a total of 13 research groups, 9 of which are run by EMBL and the remaining 4 are run by UJF/CNRS. The laboratory is located in the international research center that also houses the European Synchrotron Radiation Facility (ESRF), the Institut Laue-Langevin (specialized in neutrons) and EMBL. The 9 EMBL groups were evaluated directly by EMBL in 2009, and the current evaluation concerns the remaining 4, which are run by UJF/CNRS. It is important in the future to consider a single evaluation of the whole UMI, since the groups are heavily interconnected and the science is made through strong interactions within the UMI, as attested from the list of publications.

The field of activities of the groups evaluated is in structural biology of human pathogenic viruses, both doing fundamental mechanistic studies and also applications to find ways to identify new therapeutic or preventive tools to combat these pathogens.

- Management team

The UMI is headed by Steve Cusack but the UJF/CNRS part of the UMI is essentially managed by Rob Ruigrok, who heads one of the four research groups under evaluation and is Deputy Director of the UMI.

- 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)	9	10
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	6
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	8
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	7	8
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	12
N7: Number of staff members with a HDR or a similar grade	8	9

2 • Overall appreciation on the research unit

- Overall opinion

The 4 UJF/CNRS research groups of the UMI all work on important human pathogenic viruses (influenza virus, rabies virus, paramyxoviruses, HIV, Epstein-Barr Virus, adenoviruses, among others) and their host-cell interactions. They have provided several landmark results in understanding the structural biology of these pathogens. They have also contibuted important technological developments that are now accessible to the structural biology community at large, and at the same time they take advantage of specific developments made within the Partnership for Structural Biology (PSB), which incorporates synchrotron and neutron sources for biological studies, as well as state of the art protein production, biophysical studies and crystallogenesis facilities. The laboratory benefits from a unique combination of scientists from the University of Grenoble, the CNRS and the EMBL on the international campus.

Major contributions in the evaluation period have been the rabies virus ribonucleoprotein complex (Science, 2006), the influenza virus polymerase (Nature, 2009), the ESCRT components and their interactions (Dev. Cell 2006,Science 2008) the tetherin structure (in press), and structural insights on the cellular polymerase III (Mol Cell 2007), among others. These important achievements rank this laboratory at the forefront of structural virology.

- Strengths and opportunities

Major strengths are the quality of the principal investigators, the pool of students and post-docs that they can attract, and the vicinity of state of the art facilities for structural biology. An additional potential strength is provided by the connexion to the Grenoble « Centre Hospitalo Universitaire » (CHU), although the current setup does not take full advantage of the opportunities opened by this situation.

- Weaknesses and threats

The challenging nature of the projects that are undertaken includes a risk that they may turn out not to be feasible in spite of huge efforts, but this threat is inherent to any laboratory working at the cutting edge of science.

There appears not to be enough communication between the Unit and UJF. In addition, the Unit lacks a clear strategy to make the best use of the interaction with the CHU.

- Recommendations to the head of the research unit

✓ To keep up the impressive effort to integrate the community of structural biologist in the Grenoble area.

✓ To make every effort to minimise the division between the EMBL and the « French » part of the UMI.

✓ At the local level, to improve communication with the scientific council of the University.

✓ To define specific projects that will take full benefit of the combination of their outstanding expertise and the unique situation of having a group that is also localized at the Grenoble CHU.

- Data on the work produced:

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

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	15
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	10
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	0,94
A4: Number of HDR granted during the past 4 years	1
A5: Number of PhD granted during the past 4 years	9

3 • Specific comments on the research unit

- Appreciation on the results

The research carried out in this Unit is at the forefront of structural biology. Not only they develop state of the art methodologies, but they also apply them to difficult projects, such as to the polymerase of influenza virus, to the ESCRT machinery of budding into multivesicular bodies, and to the replication of non-segmented negative-strand RNA viruses, which have provided results with very high impact.

The number of publications is very good (166 publications between 2005 and 2010 among which 77 signed as first or last author by a member of the Unit). For a relatively small laboratory with 4 research groups, the quality is excellent (publications in Nature (1), Science (2), Dev Cell (1), Mol Cell (1), EMBO J (1), Cell Host & Microbes (1) and many others in respected, although more specialized, journals such as J Virol. (4), Virology (5), J. Mol. Biol. (8), J. Biol. Chem (3) etc.).

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

A detailed list of the prizes and conference invitations was not provided to the committee, but the international scope of this lab is obvious from the whole context.

The laboratory is able to attract top quality students and post-docs from France and from abroad

Each of the evaluated groups presented an important number of grants from different sources (Région Rhone-Alpes, ANR, ANRS, EU, Gates Foundation, HFSP, etc).

The various groups are involved in scientific collaborations at the level of the Region Rhone-Alpes, as well as at the national and international levels.

- Appreciation on the strategy, governance and life of the research unit

The governance is totally appropriate, as are communication and interactions with the exterior although the communication with the scientific council of the University might be probably improved.

The Director of the UMI has been the motor of the integration into the Partnership for Structural Biology (PSB), a unique platform grouping the other international laboratories on campus (ESRF and ILL) as well as the french "Institut de Biologie Structurale" (IBS).The PBS is a unique structure, providing access to sophisticated methodologies that are at the forefront of the field.

The PIs of the UJB/CNRS run part of the UMI are all Professors at UJF (except for one), and several UJF Professors and Assistant Professors are members of the laboratory. All of them are involved in teaching fundamental biology and clinical virology. In addition, the PSB regularly organizes specialized courses to teach new methods in structural biology.

- Appreciation on the project

The UMI has an excellent scientific project, aiming not only to understand molecular mechanisms in virus infections, but also to develop new methods to allow the study of processes that are not yet accessible to structural approaches. The Unit is trying to reach out to do structural cell biology, but this is not its strength for the moment, and would require a heavy investment in correlated light and electron microscopy.

The ressource allocation policy appeared appropriate and relevant.

It is clear that the evaluated groups are doing original research at the frontiers of structural virology. Risks are taken but the exceptional environment warrants that many of the risky projects will result in important findings, even if the initally expected result is not obtained. This is reflected in the impressive list of previous discoveries from the laboratory.

4 • Appreciation team by team

Team 1: Replication of negative-strand RNA viruses

Team leader: M. Rob RUIGROK

- 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)	3	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	1
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)	5	3
N7: Number of staff members with a HDR or a similar grade	3	2

- Appreciation on the results

The group leader is known internationally in the field of replication of negative-strand RNA viruses. The group has provided crucial information about the viral proteins that participate in the replication of viruses in the Mononegavirales order (encompassing all of the non-segmented negative strand RNA viruses) and have also obtained important results on influenza virus, a segmented negative-strand RNA virus. They continue to carry out original research, and are turning into the study of natively disordered regions of the polymerase cofactors, such as the phosphoprotein (P) from Measles and Sendai viruses (paramyxoviruses) as well as the rhabdoviruses. Their interaction with other groups within the UVHCI on the influenza virus polymerase and on rabies virus has led to important breakthroughs (structures of Influenza virus PA protein in Nature in 2009, and of the nucleocapsid/RNA complex of rabies virus, Science 2006).

The number of publications is high (57, among which 27 signed as first or last author by a member of the group). Among the latter, there are several in high impact journals : 1 Science, 1 Nature, 1 EMBO J, 1 Molecular Cell, and several publications in very respected, although more specialized journals (2 in J. Virology, 3 in Virology, 1 in JBC, 3 in JMB and 2 in Biochemistry)

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

This group has a number of international collaborations, and has numerous interactions within France. It has been successful in attracting high-level international post-docs. They were recently joined by a University Professor with specific expertise in biophysics, adding to the methodological portfolio of the whole Unit. They also recuited a CR2 CNRS position.

The group demonstrates a good ability to raise funds, as judged by the number of grants (member of the EU « Virgil » network of excellence, CNRS « MIE » grants, ANR FLU INTERPOL grant, EU FLUPOL consortium, ANR « ANRAGE » grant).

The group has an active participation to international and national networks. Important collaborations include : The Geneva Medical School, the « Centro Nacional de Biotecnologia » in Madrid, Spain, the CNRS at Gif-sur-Yvette, Institut Pasteur in Paris, Institut de Biologie de Lille (France) ; IBS (nearby in Grenoble)

This group has provided important mechanistic knowledge on the replication of negative-strand RNA viruses. Such knowledge can be used in translational application to identify efficient antivirals for a number of pathogenic viruses that belong to this category.

- Appreciation on the strategy, governance and life of the research group

The organization of the group appeared totally adequate, including governance and communication, both interanl and external.

The group participates in highly relevant initiatives in the Grenoble area, the most important one being the creation of the Partnership for Structural Biology (PSB), which is unique in Europe.

The PI and one of the group members are full Professors at UJF, and as such are involved in intensive teaching. An assistant professor (« maitre de conférence ») is also member of the group, garanteeing fluid contacts with students. The PI participates in a joint teaching program together with other members of the Unit, teaching basic and clinical virology.

- Appreciation on the project

The project will continue the highly successful research on negative-strand RNA virus replication. A specific focus will be on the RNA polymerase complex of the Orthomyxoviridae (influenza and Thogoto viruses) and on the nucleocapsid and polymerase of Mononegavirales. These projects will take advantage of the local expertise in electron microscopy and X-ray crystallography. The group plans to expand the research into cellular aspects, by incorporating light microscopy together with other biophysical approaches.

- Conclusion

  - Overall appreciation

The group is excellent, working at the cutting edge of its field. Its research is highly original and internationally recognized

  - Strengths and opportunities

Quality of the past research, resulting in high impact publications during the last four years

The project is both ambitious and realistic.

The scientific and technological environment is optimal.

  - Weaknesses and threats

The very ambitious nature of the project of course raises the possibility of failing in specfic parts. This is more of a threat than a weakness, but even in this case, there's bound to be important results

  - Recommendations

The main recommendation is to maintain the excellent scientific level that the group has demonstrated in the past.

Team 2 : Structural biology of enveloped virus entry, assembly and budding

Team leader: M. Winfried WEISSENHORN

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

	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	2
N7: Number of staff members with a HDR or a similar grade	1

- Appreciation on the results

This group has made a number of very important contributions concerning the structure of viral fusion proteins in the past. This work was later extended to viral matrix proteins and more recently to the cellular ESCRT machinery involved in multivesicular body formation and in budding of many enveloped viruses. In recent years, the group has concentrated on human immunodeficiency virus.

In the last few years, the group has made important contributions in particular concerning the structure and function of ESCRT components with a particular focus on ESCRT III proteins. They have solved the structure of the CHMP3 protein and showed that CHMP2 and 3 can form regular tubes that are likely to be involved in membrane bending. In collaboration with an internationally leading group working on HIV assembly, they tested various

hypothesis based on their structural work. Further important contributions concern the design of potential vaccine antigens to induce broadly neutralizing responses and the recent achievement of solving the structure of the extracellular domain of the HIV restriction factor tetherin.

With these achievements, the group has maintained its internationally leading position in this field and certainly belongs to the top 5 groups working on this topic worldwide. Their research is highly original and leading the field.

The group has a very strong publication record. The number of publications is not particularly high (26 publications in peer-reviewed journals of which 18 are signed as first or last author), but the majority of publications has appeared in leading journals and some in high impact journals (2 x Science, 1X Dev. Cell, 1 x PNAS, 1 x Cell Host & Microbes) with two currently submitted publications (presented at the evaluation) also likely to appear in high impact journals.

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

The group is clearly highly attractive for foreign students and postdocs and has recently attracted a CNRS CR1 position. Several of the postdoctoral fellows have won highly competitive international support (EMBO. HFSP fellowships).

The group has been highly successful in raising grants both in the French system (ANR, ANRS) as well as on an international scale (EU STREP, Deutsche forschungsgemeinschaft). It has also won an important grant from the Gates foundation on HIV vaccines and has industrial support as well.

The group has a number of very strong international collaborations as well as many national and local collaborations.

Working on HIV, the group targets a problem of very high socio-economic importance on a global scale. While the research on ESCRT and tetherin does not directly target antiviral approaches, the results may clearly feed into drug development in the future. Quite obviously, the project on designing novel antigens to elicit broadly neutralizing antibodies against HIV is of utmost importance and – if successful – would have tremendous impact.

- Appreciation on the strategy, governance and life of the research group

The group appears to be very well organized with frequent and clear communication and a strong interaction.

The head of the group is professor at UJF and involved in teaching both at the University and within the graduate program.

- Appreciation on the project

The proposed project will continue the highly successful research on HIV entry, ESCRT function in HIV release and will expand on the recently initiated tetherin project. All of these research questions are of highest scientific relevance and the proposed projects are of high international standards. The program is well balanced and all medium- and long term goals appear to be realistic.

- Conclusion

  - Overall appreciation

This is an excellent group with an internationally leading position in its research field. Both the past record and the future program are of highest quality.

  - Strengths and opportunities

Very strong research program

Important contributions to the field published in high impact journals

Strong interaction with other members of the unit and highly interactive international network

The group has a good chance of maintaining and even expanding its internationally leading position in the field and will thus be a great asset to the unit, but also to UJF and the Grenoble research community in general.

– Weaknesses and threats

✓ Individual subprojects may not always lead to solvable structures, but this should be compensated within the overall project.

✓ Of course, there is the threat that all efforts to develop novel HIV vaccine antigens to elicit broadly neutralizing antibodies may not be successful.

– Recommendations

The group has a very strong research performance and should have a leading role in future development of the unit and of the Grenoble research environment in general.

Team 3: Virus Structure and Developments in Electron Microscopy

Team leader: M. Guy SCHOEHN

- 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)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1+3*	1+3*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0 (1**)	0 (1**)
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0 (1**)	0 (1**)
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	1
N7: Number of staff members with a HDR or a similar grade	2	2

* codirected with other group heads

** at IBS

- Appreciation on the results

The group's research is mainly focussed on the topic of Adenovirus assembly and virion architecture. Based on their earlier work combining EM results with X-ray crystallography to calculate a structure for the capsid of human adenovirus type 5 at quasi-atomic resolution, they now thoroughly confirmed the localization of the minor proteins in the capsid using antibody labeling and comparing the results with a different adenovirus serotype. Recently, they determined the first 3D structure of a non-human adenovirus - a work highly relevant for gene therapeutical applications. Another focus of the group was on the structures of various macromolecular assemblies. All their work findings have lead to publications in internationally recognized journals. Furthermore, the group has been involved in numerous high quality collaborative research projects with UVHCI groups. Two very successful examples for that are the collaborations on negative-strand RNA viruses nucleocapsid organisation and the structural analysis of the interaction of ESCRT components, that resulted in publications of the highest impact.

The number of publications is high (44, among which 11 signed as first or last author by a member of the group). Among the publications, there are several in high impact journals. Among the latter, 1 Molecular Cell, 1 EMBO

J. and several publications in very respected, although more specialized journals (2 in J. Virology, 2 in Virology, 1 in J. Biol. Chem, 1 in J. Mol. Biol.). Notably, the group's contribution in collaboration with other UVHCI groups has lead to 2 publications in Science in the review period.

This group has a strong collaborations with many other groups in the UMI, including those in the EMBL part. Indeed, the EM platform provided by the group acts as a nucleation center that often develop into further fruitful collaborations.

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

The group provides the EM platform for UVHCI, the whole international campus and beyond. This specific expertise adds to the methodological portfolio of the whole Unit and gives the group a crucial relevance for the local research success. Furthermore, this group has numerous scientific interactions within France and a collaboration with a group in Canada.

The group was only recently constituted formally. There are currently no PhD students. They have been able to recruit one international post-doc. Given the attractive research programme at the interface of structural and cell biology it is highly likely that they will be able to attract new strong group members. The strategic direction towards cell biology is comforted as a CR1 scientist has recently joined the group. His integration will likely be very fast and smooth as the goup has been collaborating with him before, as documented by several joint publication.

The group has been able to raise 3 grants independently (incl. 1 with an industrial partner) and is coapplicant for numerous grants by other UVHCI and IBS groups to support the joined supervision of postdoctoral fellows. The group has a good ability to raise funds as demonstrated by the coordination of the purchase of the 'Polara' microscope (>2 M€).

Members of the group fullfill the specific and long standing role to provide EM expertise for the international campus in Grenoble. Given the short time after the formation of the group the active participation in international and national networks is currently mainly through join applications with UVHCI partners. The potential for independent participation in such networks is clearly there.

The group has provided crucial insight on the organisation of the Adenovirus capsid. With Adenoviruses beeing used as vectors for gene transfer and therapy, this field holds large potential for translational applications. Two patents based on the adenovirus work of the group have been filed.

Additionally, there is one joint grant with Merial on the 'Hyperbar project'. This development is confidential and was therefore not covered in the material available for this review.

- Appreciation on the strategy, governance and life of the research group

This group became independent during the period being reviewed (it used to be part of team E1). The team is still in the phase of establishing and structuring itself, but the directions of intended crucial enforcement of the team are clearly defined and adequate. The planned move of IBS onto the international campus will be particularly benifitial for this group. This move will terminate the difficult split between the two sites and will bring the electron microscopes all onto one site. The organization of the laboratory is adequate and integration of the engineer and technical position in IBS is very good with defined responsibilities.

Highly relevant initiatives in the field of electron mIcroscopy have been undertaken by this group in Grenoble. The most recent is the coordination of the purchase of the new 'Polara' 300keV field emission microscpe with energy filter (just delivered ; second of its kind in France), the purchase of a robot for sample vitrification, and the equipment of the screening microscopes with digital cameras. Currently, the capabilities for correlative light and electron microscopy are under implementation.

The group provides – mainly via the associated IBS technician – a crucial service in negative staining and sample characterisation highly relevant for all other groups in UVHCI. There is no formal university teaching activity of group members.

- Appreciation on the project

The suggested program will on one hand continue the successful research on the main focus of the group: adenovirus structure. A valuable extension towards cell biological aspects and the planned integration of light microscopy, allowing to adress structure function relationships and dynamic processes directly, is planned and first steps towards this aim have already been taken. This is a highly attractive move and reflects very much the aim of the unit as reflected in its its name, i.e. to understand virus-host cell interactions. The project has the strength to be fruitful and successful as a a long-term focus. The technological developments undertaken in this context can then be rolled out and made available to other group's projects. A second specific focus is on the organisation and assembly of negative-strand RNA virus nucleocapsids. Here an elegant in vitro investigation system has been established in the group by one of the members. This system will allow a thorough analysis of the complexes and will benefit also from the tomographic imaging possibilities becoming available with the arrival of the 'Polara' microscope.

The research of this team is highly original and the scientific and methodological developments internationally cutting edge.

- Conclusion

  - Overall appreciation

Very strong and important group for the concept of UVHCI and the whole campus.

  - Strengths and opportunities

The group provides EM as a crucial technological platform and as such has an important role for the very succesfull unit and the international campus at large.

Its complementary contributions to the high resolution imaging has in the past resulted in high impact publications.

The targeted development towards cell biology of virus infection and the development of correlation microscopy with light microscopy provides great opportunities.

The project is both ambitious and feasible.

  - Weaknesses and threats

The very ambitious nature of the development of the project towards cell biology poses naturally also the possibility of failing in specific parts in the short run. Even if this threat becomes serious it is worth the effort since once established this extended platform will provide numerous directions important for a truly integrative strcutural biology approach. For the implementation of the correlative light and electron microscopic imaging developments, communication and coordination with other groups on the international arena would be most beneficial.

It will be crucial for the group to keep a good balance between service, collaborations and own research activities.

Within the next years, the Head of the IBS group providing crucial image processing expertise will retire. Given the extension of the activities of the group to cryo-electron tomography that requires dedicated processing tools it has to be ensured that continued expertise in image processing will be available locally in the future.

The coverage of the service contracts costs for the Polara microscope after the 3 year initial period should be discussed well in advance and would idealy be covered by core funding through the partners involved in the purchase.

  - Recommendations

The group should continue to provide its excellent complementary EM support on campus.

An increased presence of the group on international conferences would advance the visibility of the group outside Grenoble and increase its basis for international collaborations.

Team 4 : Integrative biology of persistent human viruses (DNA and RNA viruses)

Team leaders: M. Wim BURMEISTER and M. Patrice MORAND

- 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)	5	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	1
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)	3	6
N7: Number of staff members with a HDR or a similar grade	5	4

- Appreciation on the results

This group works mainly on Epstein-Barr virus (EBV) and has additional projects on poxviruses and hepatitis C virus. It aims at integrating clinical and basic research. Main contributions in the evaluation period were the 3D structures of an EBV nuclease, dUTPase, uracyl DNA glycosidase, BARF1 alone and in complex with CSF1. This group also participated in the determination of the structure of the EBV transactivator Zebra. This structural information is now being used for the screening of small molecules as potential antiviral lead compounds. They are also using these proteins for developing novel serological tests, taking advantage of the clinical environment.

The number of publications is good (44, among which 20 signed as first or last author by a member of the group). Among the latter, 1 in JBC, 2 in JMB, 1 in Structure and, several publications in more specialized journals. However, there is no joint publication beween the two heads of the group.

During the evaluation period, the group has obtained 1 patent (Method for amplifying HCV in Aedes mosquitos. WO/2008/078056) and the extension of two more are now in progress (Mutations dans la protéine NS5B du VHC, French patent application 0854292 ; The use of synthetic peptide derived from ZEBRA protein for the in vitro diagnosis of the EBV reactivation. European patent application N° 08 290 224.8).

This group has an active collaboration with a group working in Lyon on functional aspects of EBV. They also have a number of international collaborations, in particular one in Canada on HCV IRES.

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

One researcher (CR1) from INSERM joined the group recently.

The group appear well funded as judged by the number of grants obtained

This group is participating in an international network with different companies on the exploitation of a patent, regarding EBV diagnosis. The group is also involved in the EU projects SPINE and SPINE-2

The group has obtained one patent related with a method for amplifying HCV in Aedes mosquitoes. The extension of two additional patents (one based on mutations in the protein NS5B of HCV and the second based on the use of ZEBRA for the in vitro diagnosis of EVB) is actually in progress.

- Appreciation on the strategy, governance and life of the research group

The current organization of the group does not appear to be fully adequate to support its ambition of integrating basic and clinical research. It currently appears in two largely separate parts. The Committee felt that they should intensify communication and interactions within the group. Furthermore, they should focus their research program on one or a few relevant common subjects. Because of the separation of the group in two different geographical areas, the scientific coordination is critical and could be optimized.

The permanent researchers have a very high teaching load. They contribute to a joint teaching program together with other members of the Unit, teaching basic and clinical virology.

- Appreciation on the project

The proposed project is a continuation of a previous work and is divided in different objectives:

- The characterization of new antiviral targets against EBV replication and HCV through structural and functional studies and structure-based drug design (Structural studies of the EBV helicase-primase complex; Functional studies of - EBV nuclease; Screening of ZEBRA inhibitors; Structural and functional stusies of HCV IRES).

Studies of cellular partners of EBV (BARF and ZEBRA).

- Translational research on ZEBRA for the diagnosis and treatment of EBV associated diseases.

The project appears feasible, but a more clear focus and a way of integrating the different expertises within the group should be achieved.

- Conclusion

– Overall appreciation

The group has research output (as attested by the number publications) and targets a highly relevant research topic. To increase the impact and international standing, the group has to focus. An overall vision of the main biological questions that has to be adressed during the next period is needed.

– Strengths and opportunities

Integration of basic and medical research

Good level of publications

Quality of the environment

– Weaknesses and threats

Lack of focus and coordination.

The relevance, the future perspectives and the overall integration of the HCV related project are unclear.

– Recommendations

Focus and improve coordination of the projects within the group.

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+

Nom de l'équipe : REPLICATION OF NEGATIVE STRAND RNA VIRUS

Note de l'équipe	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+

Nom de l'équipe : ENTRY, ASSEMBLY AND EGRESS OF ENVELOPED VIRUSES

Note de l'équipe	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+

Nom de l'équipe : VIRUS STRUCTURE AND ELECTRON MICROSCOPY DEVELOPMENT

Note de l'équipe	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+

Nom de l'équipe : INTEGRATIVE BIOLOGY OF PERSISTENT HUMAN VIRUSES

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

PRESIDENCE

Nos Réf. LD/GG/FT 219 -10
Tél. 04 76 51 48 29 - Fax 04 76 51 43 12

UNIVERSITE JOSEPH FOURIER
SCIENCES.TECHNOLOGIE.SANTÉ
GRENOBLE 1

Grenoble, March 29 th 2010,

AERES
Mr. Jean François Dhainaut

Subject : Comments of University Joseph Fourier Grenoble 1 on AERES preliminary report Virus Host Cell Interactions (UVHCI)– UMI 3265 - Head : Pr. Stephen CUSACK

Mr. Chairman of the visiting committee, Dear Colleague,

We have examined the preliminary assessment report dated March 4th 2010 for research unit :

Virus Host Cell Interactions (UVHCI) – UMI 3265

On behalf of the University and all members of this laboratory, we would like to express our thanks for this thorough assessment.

We are generally very pleased with the report and thank the review committee members for their useful and constructive report.

Besides, you will find enclosed in a separate document, some additional comments related to technical inaccuracies.

Yours faithfully.

P/ Le Président de
l'Université Joseph Fourier Grenoble I
Farid OUABDESSELAM

P/O Le Vice-président
du Conseil Scientifique de
l'Université Joseph Fourier Grenoble I
Laurent DAUDEVILLE

Enclosed : Some additional comments related to technical inaccuracies.

Unit of Virus Host Cell Interactions
UMI 3265 UJF-EMBL-CNRS

Dr Stephen Cusack
Director of UVHCI
6, rue Jules Horowitz
BP 181
38042 Grenoble Cedex 9

Le 30 Mars 2010

Unit director's response to the AERES draft report for UMI 3265 UJF-EMBL-CNRS.

Issues arising from the report requiring further discussion (e.g. at UMI Steering Committee meeting on June 14th). List non-exhaustive.

1. Page 3. It is important in the future to consider a single evaluation of the whole UMI.

2. Page 4, bottom and elsewhere (e.g. page 6 top); It is stated that there appears not to be enough communication between the Unit and UJF. We do not understand the comment, or why this should be the case only for UJF rather than EMBL and CNRS.

3. Page 4, bottom and elsewhere. The Unit lacks a clear strategy to make the best use of interaction with the CHU.

4. Page 6. The Unit is trying to reach out to do structural cell biology, but this is not its strength at the moment and would require a heavy investment in correlated light and electron microscopy. We agree, more resources required! See points 5 and 6.

5. Page 12. It has to be ensured that continued expertise in image processing will be available locally in the future. We fully agree (related to point 4). A CNRS candidature is in progress for such an expertise.

6. Page 12. The coverage of the service contracts costs for the Polara microscope after the initial 3 year period needs to be foreseen. We fully agree (related to previous points 4 and 5). Co-ordination with IBS required, almost certainly within the INSTRUCT framework.

7. Page 14. Burmeister/Morand team. Lack of focus and co-ordination. Relevance of HCV project? The team will be requested to come up with a focussed plan integrating CHU activities.

Stephen Cusack

Dr Stephen Cusack

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