INSTITUT COCHIN Biologie Cellulaire et intéractions parasitaires

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Department of Cellular Biology

and Host-Pathogen Interactions

of the Cochin Institute

University Paris 5

March 2009

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et de l'enseignement supérieur

Section des Unités de recherche

Evaluation report

Research unit :

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Of the Cochin Institute

University Paris 5

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

mars 2009

Evaluation report

The research unit :

Name of the research unit : Department of Cellular Biology and Host-Pathogen Interactions

Requested label : UMR CNRS, UMR_S INSERM

N° in case of renewal :

Head of the research unit : M. Pierre Olivier COURAUD

Head of the Department : Mme Claudine PIQUE

University or school :

Université Paris 5

Other institutions and research organization:

INSERM

CNRS

Dates of the visit :

December 8-10, 2008

Members of the visiting committee

Chairman of the commitee :

M. Vincent LOTTEAU, Université Lyon 1

Other committee members :

M. Thomas PIETSCHMANN, Hannover, Germany

Mme Marie-France CESBRON, Université Joseph Fourier, Grenoble

M. Jérôme ESTAQUIER, IMRB, Paris

M. Jean-Louis MEGE, Université Aix Marseille 2

M. Pierre JALINOT, ENS Lyon

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

Mme Elena LEVASHINA, Strasbourg, CSS INSERM representative

Mme Mounira CHELBI-ALIX, Villejuif, CoNRS representative

M. François FREYMUTH, Caen, CNU representative

Observers

AERES scientific representative:

M. Marc BONNEVILLE

University or school representative:

M. Bruno VARET, Université Paris 5

Mme Marie-Christine LABASTIE, Université Paris 5

Research organization representatives :

Mme Christine TUFFEREAU, INSERM

Mme Evelyne JOUVIN-MARCHE, CNRS

Specific appreciation team by team

Team 1 : Viral proteins and intracellular trafficking

This team is co-directed by one DR2 CNRS and one CR1 INSERM. The present project is organized along three major axis :

1. The study of intracellular trafficking at the primary cilium, extending their original observations and expertise on beta-arrestins and clathrin-mediated endocytosis.
2. The role of HIV-Nef with a strong orientation toward the analysis of its interference with the endocytic pathway.

The development of new anti-viral strategies based on previous observations and proof of concept, especially by targeting CD4-Scramblase interaction and production of single-domain antibodies against HIV proteins.

Strengths

With their previous projects, both leaders have independently produced good science in the field of intracellular trafficking for the latter and HIV life cycle for former PI. They both published on a regular basis in the best speciality journals (among which 5 J. Virol, 7 Traffic, 4 JBC, 1 Plos biol., 1 Plos Pathogen, 2 J. Immunol…).

Axes 1 and 2 are in the logical continuum of each leader's scientific interest, asking up-to-date questions relevant to cell biology and viral infection.

There is a mutual involvement of each leader in both projects. The DR2 is also in charge of the anti-viral strategy project while the CR1 appears more implicated in the organization of teaching and M2 program.

Although not involved in a major european network or clinical trials, there is a good fund raising in support of the different projects with several collaborations inside and outside the institute.

Transfer of technology is also good for this team, especially for TIRFM.

Weaknesses and recommendations

Considering the cutting edge anti-viral project, a partnership with the industry has not yet been developed but this could be a recommended option to make sure that the project will not stop before having shown its potential.

In conclusion, based on previous experience of both leaders and on the quality of the submitted projects, the committee strongly believes that this team should be successful in the achievement of their goals.

Nom de l'équipe : Proteines virales et traffics intracellulaires

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

Team 2: Host Virus interactions

The key objective of this team (with two leaders) is the identification and functional characterization of host factors that are crucial for HIV replication. More specifically, the two subgroups comprised in this team focus on the early and late steps of HIV replication which involve transfer of the viral pre-integration complex (PIC) into the nucleus, integration and tat-dependent transcription as well as envelope-gag protein interaction and virus egress.

Strengths

Both subgroup leaders are nationally and internationally very well recognized experts in this field of research. Their work has substantially contributed to our understanding of the interplay between HIV and host proteins in the course of integration, early transcription and viral egress. The excellent standing of these two group leaders is based on a long-standing track record in the field as well as the recent identification of LEDGF/p75, SWI/SNF, TIP47 and AP-1 as important host factors for HIV replication which is a remarkable testament of the originality and success of their research efforts. These findings have not only opened new perspectives for future research on fundamental aspects of HIV-cell biology but in addition highlighted novel possible targets for anti-viral intervention. Therefore, their contribution has had a very significant added value for the field and will stimulate cutting edge basic and applied research.

A substantial number of recent publications with the group leaders as senior authors not only in top journals of the field (e.g. Mol Biol Cell, 2 J Biol Chem) but also in high impact journals with broad scope (1 EMBO J, 2 PNAS) are an impressive token that both groups are very successfully competing at the forefront of their field.

As a consequence of their long-term commitment to this field of research both group leaders are very well connected at the national and international level. In particular their involvement in three different EU-funded research networks and importantly the entrustment of the coordinating role in one of them reflects the extraordinary degree of integration into research collaborations at the international level.

Besides this, the group has successfully established a strategic partnership with CellVir SME, Evry, France, which includes funding of a technician by the industry partner. The team has filed patents on the Ma-Tip47 and the In-LEDGF interactions and granted licenses to operate for CellViro. The partners have identified a number of lead compounds that are promising candidates for future development as novel HIV integrase inhibitors. Together these indicators thus clearly document a very strong translational aspect of the research of the team.

The tight international bonds in academia together with the direct bridge to an industrial partner and the balanced structure of the group consisting of a stable mixture of postdocs, PhD-students and technicians, are not only a clear indication for strategic planning and intelligent management, they also hold an excellent promise for future stability and prosperity of the team.

The proposed project is a direct and logic continuation of their previous very successful research. The technologies employed are fully within the key competences of the group. The individual workpackages are well planned and the aims of the project and the overall direction is highly relevant both for basic and applied HIV research.

Thus, in conclusion this team of two self sufficient, successful, and internationally very well recognized and competitive group leaders holds excellent promise for further development which should be supported by allocation of sufficient resources for further growth.

Recommendations

In the long term, for their own personal career development, the team leader may consider aspiring fully independent group leader positions to further enhance their individual visibility. However, this is of course a personal decision of the group leaders and it should not be pursued at the expense of the prosperous interactions of the subgroups.

Nom de l'équipe : Host-Virus interactions

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+

Team 3 : Mucosal entry of HIV and mucosal immunity

This group is composed of one CNRS (DR2) and INSERM (CR1) staff and three post-doctoral fellows. The group's international reputation is based on his long-standing study of mucosal immunity, in particular on the role of IgA. The CR1 researcher joined the group at the end of 2008, and the proposed project is to address the role of the HIV co-receptor CCR5. Thus, in a certain manner the strength of the existing project has not been reinforced and the rationale about CCR5 in the gut for HIV entry seems to be minor in comparison to the other routes described by the DR2. The part of the project regarding the mechanisms of entry by using tissue explants and model of 3D reconstitution to study the role of human foreskin appeared very interesting. The project also consists in the analysis of the immunogenicity of several peptides derived from the gp-41 that could be a target for neutralizing antibodies. Based on virosome, a phase I project will be conducted in Belgium to test the impact of these peptide structures. Although, the other projects mentioned by the DR2 are also addressing important question they may dilute the activity of this small team and reduce the impact of the main project on HIV.

Strengths

A small dynamic group with a proven track record in mucosal immunology.

The publication record is good (PNAS, Mol Cell Biol, Faseb J, 2 AIDS, etc.. for the DR2 ; 2 Mol Pharmacol and J Biol Chem for the CR1) but could be improved as it does not really reflect the quality of the work.

The team has issued 4 patents, is involved in one EEC network.

Team leaders have been invited in several international meetings, have established numerous national and international collaborations and good connexion with the industry.

Strong funding from the ANRS and Europe community.

Weaknesses and recommendations

The program proposed is quite ambitious (numerous tasks), and may appear large in its scope given the current size of the group and the level of international competition. In particular, the development of a second axis based on the study of CCR5 could possibly lead to a dilution of its potential. One way to maintain and increase the competitiveness of the team would be to remain focused on the initial objectives.

Also remain focused and increase the quality of publications to better match with the quality of the research.

Nom de l'équipe : Mucosal entry and HIV immunity

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

Team 4 : Phagocytosis and bacterial invasion

This team is composed by two scientists, two post-docs, five PhD students and one contract research assistant; the two scientists are leading the team.

The PIs run two quite distinct projects. The first project (internalization by specialized phagocytic cells) is based on the previous project but it extends it towards new domains. Whether the dissection of receptor-mediated phagocytosis will be continued, the mechanical forces generated during phagocytosis will constitute a new field with a transversal approach (collaboration with physicists). Two sub-projects are issued from the major project. One will analyse the hijacking of cell machinery by Nef HIV-1 and the other the interaction of dendritic cells with B cells. The second project can be divided in two sub-projects. One is the extension of the previous project and will result in the study of type IV pili receptors by pertinent strategies. The other concerns the mechanisms of Erb2 activation. Erb2 makes a link between cancer and infection and the scientist will assess the role of Erb2 in breast cancer.

Strengths

Each scientist has excellent originality and notoriety, which are supported by excellent publications (14 publications including 3 J Cell Biol and 5 publications outside the Institute for one leader). Only one publication (J Cell Biol) was signed in common. The contributions of each scientist have brought new and important insights into the knowledge of host pathogen interaction. For one, the study of phagocytosis mechanisms revealed the importance of molecules associated with endocytosis and cytoskeleton and the hijacking of cell machinery by pathogens. The other reported the cellular events associated with the invasion of endothelial cells by Neissseria meningitidis. These latter findings show the common mechanisms used by eukaryotic cells and pathogens to interact with endothelium.

These two projects should benefit from tight interactions with Virology and Immunology teams of the Institute.

The contribution to training programs (Master, PhD, Post-Doc) and to scientific diffusion is good.

Similarly, the scientific cooperations are well developed.

Weaknesses and recommendations

The transfer of technology was relatively poor but easy to understand because of the importance of basic projects.

The projects of each scientist are good but quite heterogeneous.

The Erb2 project is very competitive and the scientist should develop strong collaborations with researchers in human oncology. This sub-project possesses the potential for transfer technology to clinical fields. These projects are important but they are not high risk projects.

The future of the team deserves some comments. The team has a deficiency in young researchers besides the two leaders and in research assistant. The management of the team reveals two leaders of high scientific quality with two distinct programs whose merging brings limited added value. Although both tried to establish collaborations, they failed, which excludes a recommendation of mixing both programmes.

Improve the attractiveness for young researchers

The budget of the team should be strengthened.

The two leaders should strengthen what is their specificity (cell biology of phagocytosis and bacterial invasion) and develop tighter interactions with other teams of the Institute for the other projects.

Nom de l'équipe : Phagocytose et invasion bactérienne

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

Team 5 : Molecular mechanisms of sepsis

This team focuses its research on the molecular mechanisms of sepsis with the aim to identify factors that underlie the variability of the innate immune response to an infectious challenge. The field-specific long-term research activities are based on clinical and experimental approaches.

Strengths

The team has identified and successfully exploited an excellent niche provided by the quality of the cohorts, which makes it highly competitive in the field of innate immunity. There is no doubt that the established data banks will be a unique asset in the present and future research of the Team. This work is part of the European FP6 program GenOSept, where the Team is crucially contributing to investigate genetic factors that influence the outcome of community acquired pneumonia.

Weaknesses and recommendations

The upstream experimental projects that investigate mechanisms of sepsis-induced immunosuppression, appear less advanced and isolated as compared to the clinical side. Although it is still too early to assess fully the added value brought to the team by the arrival of a CR1, these projects need to be strengthened by interactions with specialists in innate immunity within (for instance, but not only, the dendritic cell team from the immuno-hematology department) or outside Cochin. The murine model of secondary pneumonia has already provided interesting results in respect to decrease in numbers and maturation abnormalities in spleen dendritic cells, however development of additional in vitro or in vivo physiopathological models might be more directly relevant to the clinical programs, for instance studies of interactions between S. pneumonia and immune cells.

In conclusion, very interesting long-term project which would benefit from reinforced collaborations and in vitro models relevant to the clinical studies.

Nom de l'équipe : Immunité Innée

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

Team 6: Comparative biology of apicomplexan parasites

In the context of several collaborations, the team, headed by a senior researcher with a DR1 CNRS position, is addressing several interesting parasitological topics using three different parasite species as models. The original studies on the Theileria-induced leukocyte transformation demonstrated how the parasite manipulates both the JNK1 and JNK2 signalling pathway to accomplish its parasitic cycle. These findings have opened up the possibility for the team of developing an engineered attenuated vaccine against tropical theileriosis. The team leader also presented a series of ongoing ambitious collaborative projects on Toxoplasma and Plasmodium parasites. These include the role of Plasmodium PKA as a regulator of erythrocyte anion channel, studies of the PKA-signalling in Plasmodium vesicular transport and the systematic functional analysis of rab GTPases in both Plasmodium and Toxoplasma using reverse genetics.

Strengths

The good record of publications of the team leader over the last 4 years (a total of 21 publications including 3 Cell Microbiol., 1 Cancer Res., 2 PLoS Pathogen and 6 review articles) clearly demonstrates the dynamism of this researcher in developing fruitful international collaborations.

Weaknesses and recommendations

The committee failed to identify a clear input of the team in all of these projects in terms of experimental expertise.

The committee also felt that the described projects are too big for the current size of the team and therefore lack critical mass necessary for success.

Although most of the proposed projects rely on a number of high-ranking collaborations, it was unclear to the committee which of these projects will be developed locally by the team and which project constitutes its main focus.

In conclusion, while it is appreciated that the team leader is highly dynamic and involved in many collaborative projects, a recommendation could be to refocus the major research project and to re-define the program of activities to ensure a successful development and progress of the team local expertise.

Nom de l'équipe : Biologie celullaire comparative des apicomplexes

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	B

Team 7 : Virus-Cell Molecular Interferences

The team "Virus-cell molecular interferences" is a young team established since 2005, one of its leader benefiting from an INSERM "Avenir" program. It is composed at present of 1 CR1, 1 DR2, 1 MC, 1 post-doc, 4 Ph. D. students and 1 technician. The main interest of the team is to elucidate the function of HIV and HBV auxiliary proteins. In the past years important contributions have been made to the field, in particular by showing that the HIV-1 Vpr protein interacts with DCAF-1, an adaptor protein of the Cul4A-DDB1 complex. This interaction is important for the cytostatic effect of Vpr. They have also shown that HIV-2 Vpx by interacting with DCAF-1 overcomes a restriction factor in the infection of macrophages. In the frame of this team one of the group leader has signed as last author four publications in J Biol Chem, Cancer Res., Cell cycle and Plos pathogens.

The main question the team wants to answer in the future is the nature of the cellular targets of which degradation is induced by these viral auxiliary proteins. In addition to the HIV Vpr, Vpx and Vpu proteins, investigations will also be conducted on HBV HBx which has been shown to interact with DDB1. To study these questions the team plans to use both proteomic and candidate protein approaches.

Strengths

Recent interesting observations made by the team leaders, who have a good track record.

Weaknesses and recommendations

With respect to the project, the committee may recommend to widen the approaches and also to confront carefully the results obtained in model cell lines with natural infection situations.

The team is also invited to engage in more international collaborations and networks.

Finally, additional interactions with the other groups at Cochin working on HIV would certainly be beneficial.

Presently, it does not appear that the acquired knowledge can be used in a translational perspective, but if in the future targets of interest are found it will be important to consider this aspect more carefully.

Concerning the management of the team the added value of a shared direction is not obvious.

Finally the HBx protein project seems somewhat out of focus and it is questionable to maintain this program in addition to the other HIV-1 subjects.

Nom de l'équipe : Virus-cell molecular interferences

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

Team 8 : Cellular partners of human retroviruses

Team 8, headed by a DR2 CNRS, includes 3 permanent scientists (1 DR2 CNRS and 2 CR1 CNRS), 1 post-doc and 1 PhD student. The main focus of this team is the characterization of cellular proteins that regulate the replicative cycle of the Human T-cell Leukemia Virus type 1 (HTLV-1) which is the etiological agent of the adult T-cell leukemia. This group discovered that Neuropilin 1 (NRP-1), a co-receptor for Vascular endothelial growth factor (VEGF165), functions as an HTLV-1 receptor. It found also that HTLV-1 envelope mimics VEGF165 to interact with NRP-1 and that NRP-1 cooperates with GLUT1 and heparan sulphate proteoglycans to promote entry. This led to proposal of a new model for HTLV-1 entry in which the receptor is a multiprotein complex. This team also shows the importance of post-translational modifications on Tax functions. Tax ubiquitination governs its ability to activate NFκB pathway, a critical event for HTLV-1-induced cell immortalization. Ubiquitination leads to formation of a Tax/IKK complex anchored to the centrosome. It has also been shown that Tax interacts with members of the TRAF family which might be responsible of Tax ubiquitination. In parallel, this team showed that human Discs large (Dlg1), a scaffold protein implicated in the formation of multiprotein complexes at the plasma membrane, is a new binding partner of HIV-1 Gag. Dlg1 depletion in producer T cells enhances particles infectivity. To understand this effect, the team wish to study the role of Dlg1 on the cell-to-cell transmission of HIV-1 and the relationship between Dlg1 and the HIV-1 protein Vpu.

Strengths

The group has actively published during the last 4 years, 12 papers in good journals : Leukemia, J. Cell Sci., J. Virol., Blood, Oncogene, Mol. Biol. Cell, PLoS Pathog, Retrovirology).

Its results have been presented in various international meetings.

Good fund raising activity and solid collaborations in the HTLV-1 field with national and international teams.

This team has gained international recognition for its contribution on HTLV-1 research that has been consolidated with the recent reinforcement by 2 permanent positions, CR1 CNRS, who have joined the group, and needs to be maintained.

In sum, the overall assessment for this team is very good.

Weaknesses and recommendations

Although it is understood by the committee that financial support might be more difficult to obtain for basic HTLV-1 virology, this team should keep and reinforce its well-recognized expertise in this field and avoid diluting it with implication in new HIV projects.

Nom de l'équipe : Partenaires cellulaires des retrovirus humains

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	B

Team 9 : Barriers and Pathogens

This team is the result of the merging of two small teams according to Institute's recommendations. The team "Molecular Pathogenesis of group B Streptococcal infections is headed by a senior researcher with a PU-PH position while the team "Motility and Cellular Invasion", is headed by a senior researcher with a DR2 CNRS position. The new team is co-headed and also includes five researchers from University and Hospital (with variable time of involvement in research), three post-doc, four PhD students and two research assistants. For historical reason, the past of each team has to be assessed individually. The team "Molecular Pathogenesis of group B Streptococcal infections" represented 50% of the activity of the leader who is also involved in clinical microbiology. The team described the epidemiologic importance of one clone of GBS in neonatal infections, the role of oxidative response in virulence and the incorporation of fatty acids in GBS membrane with the treatment applications. The team "Motility and Cellular Invasion" is a small team that was established as an ATIP CNRS and has now reached its own capacity of financial support (ANR and EC funding). This team has shown that Toxoplasma gondii exploits both CD11c+ and CD11b+ cells as shuttle vehicles to travel from the intestine to the central nervous system. Current on-going projects are re-evaluating the dogma which stipulates that the host cell is inactive during the invasion process driven by apicomplexan parasites. The project of the new team is based on common technological approaches that will be shared by the two former teams. They plan to use intravital imaging systems to understand the mechanisms used by both BGS and Toxoplasma to cross BBB. The team will use the facilities of another Institute to develop the project. This latter point has been considered as an advantage by both leaders. Each leader will keep their specific on-going projects such as the resistance of GBS to oxidative stress, the incorporation of fatty acids and the dissection of host cell invasion by Apicomplexa parasites. The intravital project is important to understand the pathophysiology of both GBS and Toxoplasma infections. It will allow a better dissection of cellular events that unable these pathogens to reach the central nervous system.

Strengths

The originality of the activity and the notoriety of the research team "Molecular Pathogenesis of group B Streptococcal infections" are good. This statement is supported by 35 publications in which 20 concern directly group B streptococcal (GBS) infections; good publications in Microbiology which are largely collaborative. A recent publication in Nature must be highlighted. There is a real added value to the knowledge. The scientific collaborations of this team, contribution to the training and dissemination of scientific culture are good.

The team "Motility and Cellular Invasion" has done very novel findings in the field of apicomplexan parasite cell biology and some of them have been published in excellent journals (Blood, PNAS). It has also recently discovered that the host cell actin also contributes to this process. There is no doubt that it would represent a very important contribution in the field (recent publication in Cell Host and Microbes).

The common approaches proposed in the project will benefit from the combined expertises of one team in experimental animal model and of the other, in cell imaging.

Weaknesses and recommendations

The presence of young researchers within subteam #1 has not been clearly shown and the partnership with industry has not been developed although the projects were adapted to such an approach.

In conclusion, the team will develop a common strategy to answer to important medical questions of pathogenesis while they will keep their own traditional strength and topics.

Nom de l'équipe : Barrières et pathogènes

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

UNIVERSITÉ
PARIS DESCARTES

Le Président
Axel KAHN

Paris, le 17 avril 2009

DRED 09/n° 172

Monsieur Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport du comité de visite concernant l'Institut Cochin « **Department of cellular biology and host-pathogen interactions** » rattaché à mon établissement.

Ce rapport n'appelle pas de commentaire particulier de la part de l'Université.

Je vous prie de croire, Monsieur le Directeur, à l'expression de ma meilleure considération.

Le Président de l'Université

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Paris, le 10 avril 2009

Réponses au rapport du comité d'experts

Report from the visiting committee

Research unit :

Department of Cellular Biology and Host-Pathogen Interactions

of the Cochin Institute

University Paris 5

The research unit :

Name of the research unit :

Requested label : **UMR CNRS, UMR_S INSERM**

N° in case of renewal :

Head of the research unit : **M. Pierre Olivier COURAUD**

Head of the Department: **Mme Claudine PIQUE**

University or school :

Université Paris 5

Other institutions and research organization:

INSERM

CNRS

Dates of the visit :

December 8-10, 2008

Team 3 : Mucosal entry of HIV and mucosal immunity

The CR1 working on CCR5 trafficking with a technician and a post doc fellow has integrated the team 3 only a year ago. This project on CCR5 trafficking is funded for another year. Thereafter, the CR1 will entirely focus on one of the initial objectives of the team, namely the mechanism of HIV transmission at mucosal sites and investigate in polarized cells the role of CCR5 in mucosal entry of HIV.

Team 4 « Phagocytosis and Bacterial Invasion »

In response to the « weaknesses and recommendations » mentioned by the AERES committee, we would like to bring up the following new informations :

- the two PIs who supervise the team have been recently selected for « Directeur de Recherches » positions at CNRS (rank 1st and 3rd, « *commission* » 24).
- the team was recently strengthened by the arrival of an Senior Research Assistant with an INSERM position (« *Assistant Ingénieur* ») and a post-doctoral researcher who got a two-yrs fellowship by the « *Fondation pour la Recherche Médicale* » (FRM) to support her second post-doc in France.
- Several additional grants were obtained since the report :
    - a « subvention fixe » from ARC (« *Association pour la Recherche sur le Cancer*», 50 k€ for 2 years),
    - an extension of the ATIP grant (« ATIP plus », 40 k€ for 2 years) and
    - a project has been recently selected to be funded by a grant from the National Research Agency (ANR Blanc 2009, in collaboration with Dr Xavier Nassif, Institut Necker, Paris).
    - in addition to existing internal collaborations, a new collaboration has been developed with the team « Immunopathology of the Heptatitis C Virus », from the Immuno-Hematology Department of the Institute, which is supported by an exploratory grant from Institut Cochin to support Inter-Departmental collaborations (« *PIC , Projet Inter-Equipes Cochin* », 15 k€ for 1 year).

Finally, a patent application will be submitted very soon by « Inserm Transfert » about a molecule providing selective inhibition of ErbB2/HER2 tyrosine kinase receptor, with possible implication in breast cancer treatment.

We are confident that our team has the scientific, technical and financial stature to successfully conduct our projects.

Team 6: Comparative cell biology of Apicomplexan parasites

Weaknesses and recommendations
"The committee failed to identify a clear input of the team in all of these projects in terms of experimental expertise."

This criticism is understandable based on our recent PloS Pathogens paper that had a significant element of electrophysiology, a technique that Team 6 does not master, and as a consequence was signed as last author by our colleague from UMR CNRS 7150. Nonetheless, the first author was a Team 6 post-doc reflecting the importance of Team 6's contribution.

In contrast, the criticism is unfounded concerning the *Theileria* & *Plasmodium* Rab projects, where Team 6 has clearly had the major technical input in both these project for many years. This statement for example, is supported by a PubMed enquiry using "*Plasmodium* & Rab GTPase" as key words, and one finds that our group authors 10 out of the 15 papers listed.

"Although most of the proposed projects rely on a number of high-ranking collaborations, it was unclear to the committee which of these projects will be developed locally by the team and which project constitutes its main focus."

This unfortunate confusion is understandable when applied to development of the PKA project that is collaborative effort between 3 groups, one of which has recently been founded by an ex- Team 6 post-doc fellow.

However, the confusion is very misleading concerning the *Theileria* JNK/AP-1 and *Plasmodium* Rab projects, in whose development Team 6 plays (and has played for many years) the major role.

Team 7: Virus-Cell Molecular Interferences

Given that the creation of our team and its leadership are at stake, we would like to express our deep concern about the way the committee has reported about our scientific activities. We feel that the provided review does not accurately report: (i) the impact of our scientific accomplishments; (ii) the validity of the strategies planned to reach this goal; (iii) the respective contributions of the team leaders to these accomplishments.

About "Strengths"
Regarding the impact of our recent accomplishments in the field of HIV research, we feel that the terms "recent interesting observations" minimize our

accomplishments. Our contribution does not come down to the mere demonstration of the importance of an interaction of the Vpr and Vpx viral proteins with the DCAF1 host protein. When we became interested in studying the Vpr protein, its cell cycle arrest activity had been known for more than ten years, although it had not received any conclusive mechanistic explanation. Our team was the first to demonstrate that Vpr recruits the host E3 ubiquitin ligase Cul4A-DDB1 via the DCAF1 adaptor protein to induce the degradation of a host protein target, which is required for normal cell cycle progression. Thus, our study not only demonstrated that Vpr interaction with DCAF1 is crucial for its activity, it also unveiled a hitherto unsuspected mechanism of action of Vpr (1). We were pleased that after our work was published, seven North-American teams published similar conclusions (see review ref 2). It might be worthwhile mentioning that our work published in 2007 has been cited >27 times up to now. Our work on Vpr prompted us to study the genetically-related Vpx protein, which is specific for the HIV type 2/ SIV sm lineage. We just published our results which demonstrate that Vpx operates similarly to Vpr by hijacking the host ubiquitination machinery through the DDB1-DCAF1 E3 ligase. Here the outcome is to protect HIV-2 from a macrophage-specific restriction factor (3). This time, two studies reaching similar conclusions were published before ours. It might be of interest to mention that only one of these studies issued from the seven aforementioned groups. We feel that it provides good evidence to our reactivity in the context of a particularly strong international competition.

About "Weaknesses and recommendations"
Approaches
One recommendation is to widen our strategies for the search of host proteins targeted to degradation by our viral proteins of interest. During our oral presentation, a reviewer asked about the use of yeast two-hydrid screens. We recall our answer being that this strategy was inappropriate in our case. For the sake of clarification, we of course conducted this strategy and none of the potential candidates turned out to meet the functional criteria expected for our host protein targets. This is why biochemical approaches such as TAP tag have gained our preference. These approaches currently give promising results.
A second recommendation is to confront the results obtained in model cell lines with natural infection situations. We do not understand this comment since primary human macrophages have been our model for our study of Vpx (3,4) and since we have proposed in the future to search for a cell culture system where viral growth is clearly impaired in the absence of Vpr.

Insertion in more international collaboration and research networks
As stated in our written and oral presentations, we have set up a fruitful collaboration with clinicians involved in the follow-up of the ANRS cohort of HIV-2 -infected patients, which was omitted in the review. We were also asked to become members of the recently created AMIR (association for macrophage and infection research). Finally, one lab from the University of San Diego has engaged in a collaboration with us on Vpu.
We are considering setting up more international collaborations for the near future.

At Cochin, we are engaged in collaborations on HIV with two groups. We are open to other opportunities.

Management of the team: a shared direction

One team leader thanks the reviewers for considering her co-corresponding author status in the mentioned Cancer Res publication as a last author position. In this case, the two leaders would appreciate their co-corresponding author status, in the quoted Cell cycle 2007 and J Biol Chem 2008 publications, to be similarly acknowledged as their equal contribution to these studies. The position of one leader as a last author in the quoted Plos path. 2007 and that of the other leader in the J. Virol paper 2009 accurately reflect their greater input into the respective studies.

That being re-specified, we feel that the judgment that "the added value of co-leadership is not obvious" should be discarded. We enjoy our daily collaboration and have proven that it is very fruitful. It might actually be more synergistic than merely additive as it may occur in teams where co-leaders conduct projects with quite few actual overlap. We are both convinced that it has been instrumental to our common and rapid success despite our team being quite a newcomer in the field.

Final remarks

We are pleased that one researcher asked us to join our team since he does not only hold a permanent position at the University Paris Diderot but he is also internationally recognized in the field of anti-retroviral restriction factors (4). That in the past both leaders have worked in quite various scientific areas is not listed as a strength. Should it be considered in contrast as a weakness, we strongly hope that our publication records in our past and present research activities provide some reassurance as to our ability to co-direct innovative and productive research.

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